



# Impact of hippocampal subfield histopathology in episodic memory impairment in mesial temporal lobe epilepsy and hippocampal sclerosis

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## ABSTRACT

**Objective:** The objective of the study was to analyze preoperative visual and verbal episodic memories in a homogeneous series of patients with mesial temporal lobe epilepsy (MTLE) and unilateral hippocampal sclerosis (HS) submitted to corticoamygdalohippocampectomy and its association with neuronal cell density of each hippocampal subfield.

**Methods:** The hippocampi of 72 right-handed patients were collected and prepared for histopathological examination. Hippocampal sclerosis patterns were determined, and neuronal cell density was calculated. Preoperatively, two verbal and two visual memory tests (immediate and delayed recalls) were applied, and patients were divided into two groups, left and right MTLE (36/36).

**Results:** There were no statistical differences between groups regarding demographic and clinical data. Cornu Ammonis 4 (CA4) neuronal density was significantly lower in the right hippocampus compared with the left ( $p = 0.048$ ). The groups with HS presented different memory performance – the right HS were worse in visual memory test [Complex Rey Figure, immediate ( $p = 0.001$ ) and delayed ( $p = 0.009$ )], but better in one verbal task [RAVLT delayed ( $p = 0.005$ )]. Multiple regression analysis suggested that the verbal memory performance of the group with left HS was explained by CA1 neuronal density since both tasks were significantly influenced by CA1 [Logical Memory immediate recall ( $p = 0.050$ ) and Logical Memory and RAVLT delayed recalls ( $p = 0.004$  and  $p = 0.001$ , respectively)]. For patients with right HS, both CA1 subfield integrity ( $p = 0.006$ ) and epilepsy duration ( $p = 0.012$ ) explained Complex Rey Figure immediate recall performance. Ultimately, epilepsy duration also explained the performance in the Complex Rey Figure delayed recall ( $p < 0.001$ ).

**Significance:** Cornu Ammonis 1 (CA1) hippocampal subfield was related to immediate and delayed recalls of verbal memory tests in left HS, while CA1 and epilepsy duration were associated with visual memory performance in patients with right HS.

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## 1. Introduction

Hippocampal sclerosis (HS) is the most frequent histopathology encountered in patients with drug-resistant mesial temporal lobe epilepsy (MTLE) [1–4]. Epilepsy surgery of mesial temporal structures has opened new avenues to trace memory formation in the human brain permitting comparative analysis between neuropathological findings and cognitive function [5].

The hippocampi serve a major role in declarative memory, and patients with medically intractable MTLE have a broad spectrum of learning and memory deficits [6]. Neuropathological investigations describe different patterns of neuronal cell loss within hippocampal formation [3,7–9].

Surgery may cause significant memory decline, especially regarding verbal memory, after left temporal lobe resection, and higher neuronal cell densities of the resected left hippocampus have been associated with greater decline in verbal memory parameters [10]. Cell loss within specific hippocampal subfields (CA1, CA2, CA3, and CA4) and dentate gyrus has been associated with pre- and postoperative memory deficits [11]. However, studies on hippocampal cell loss have produced diverging evidence as to which subfield memory is specifically related

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[12–17]. For some authors, the overall pathological status of the left hippocampus, rather than the specific subfield pathology predicts verbal memory in MTLE [13]. However, more precise neuropsychological markers for right hippocampal function are needed. Moreover, epilepsy duration has also been implicated in memory impairment [17].

The impact of segmental hippocampal cell loss in memory formation remains a fundamental question [12,15,16], and subfield specific analysis of HS may help to better classify MTLE phenotypes and clinical variability [18].

The aims of this study were to analyze preoperative visual and verbal episodic memories in a homogeneous series of patients with left and right MTLE and unilateral HS and to verify their relationship with epilepsy duration and neuronal cell density of each subfield of the resected hippocampus.

## 2. Methods

### 2.1. Patients

This study included patients with drug resistant MTLE and unilateral HS enrolled into the preoperative epilepsy surgery program of the Unidade de Pesquisa e Tratamento das Epilepsias, Universidade Federal de São Paulo that underwent anterior temporal lobectomy between 2005 and 2014. During this period, 117 patients were submitted to surgery and had the hippocampal specimens available for the study. From this amount, 45 were excluded due to histopathological criteria (hippocampus without CA1 or CA4, technical issues with immunohistochemistry) and/or neuropsychological criteria (subjects with severe psychiatric comorbidities, illiterate, left-handed, or in whom the neuropsychological evaluation was not completed) for inclusion.

Patients were submitted to preoperative evaluation including long-term video-EEG monitoring on a 32-channel digital equipment (Biologic™, and Ceegraph™ software or Nihon Kohden, and Neuroworkbench software), 1.5 T MRI (Magnetom Sonata [Maestro Class] – Siemens AG, Medical Solutions, Erlangen, Germany) using an eight-channel head coil, and neuropsychological testing (IQ, memory, and language). Clinical history and seizure semiology with interictal and ictal EEG provided lateralizing information, while MRI findings and the results from neuropsychological assessment provided the ultimate lateralization of the epileptogenic zone. Patients were included only if seizure semiology, interictal and ictal EEG, MRI findings, and the results from neuropsychological assessment were concordant and then, submitted to anterior temporal lobectomy surgery. Thirty-six patients (50%) had left temporal resections, and 36 had right.

All procedures were conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Universidade Federal de São Paulo. Informed and written consent (for additional scientific investigations) was obtained from all patients.

### 2.2. Neuropsychological tests

Although all patients included in the study were right-handed, during the neuropsychological evaluation, a language dominance questionnaire [19] was applied, and only patients with typical language dominance were included. The questionnaire was a translated abbreviated version of the Edinburgh Inventory [20] composed of ten motor tasks to be done.

Patients underwent neuropsychological examination for verbal and visual episodic memories, before epilepsy surgery, including Wechsler Adult Intelligence Scale-Revised shortened version (WAIS-R) [21] to evaluate intelligence.

Verbal memory performance was assessed using the Rey Auditory Verbal Learning Test (RAVLT) [22] and Logical Memory [23]. The RAVLT requires serial learning and immediate recall of 15 unrelated words in five consecutive learning trials, free recall, and, after distraction, the patient is required to recall the words from the original

list after a 30-minute delay. The analysis was based on learning performance (total number of words learned in five trials) and delayed recall. In the Logical Memory task, the patient reads a passage and is asked to recall as many ideas as possible up to 60, both immediately after the presentation and 30 min later.

Visual memory was assessed using the Complex Rey Figure [22] and Visual Reproduction [23]. In the Complex Rey Figure task, the patient is required to copy a complex figure and then reproduce it, as much as possible, immediately afterward and 30 min later. In Visual Reproduction, the subject observes four figures – geometric sample forms (one each time), for 10 s – and is asked to reproduce them immediately and 30 min later.

Memory parameters were standardized per a normalization sample of a group of healthy volunteers, applying a correction for age and gender. The control group was composed of 178 subjects matched for age, gender, and educational level and were submitted to the same neuropsychological examination for verbal and visual episodic memories including Wechsler Adult Intelligence Scale-Revised shortened version (WAIS-R) [21] to evaluate intelligence.

### 2.3. Histopathology

Patients were selected for this study if at least one hippocampal tissue specimen from an en bloc resection of the entire hippocampus was available on assessment.

Surgical hippocampal specimens were dissected into 5 mm slices in coronal planes along the anterior–posterior axis, fixed in 10% formalin, and routinely processed into liquid paraffin. En bloc specimens were cut at 5 µm on a rotation microtome (Microm Leica Jung SM 2000 R) and stained with standard hematoxylin and eosin.

One representative hippocampal slice encompassing at least CA1 and CA4 was chosen from each subject for quantitative neuronal cell counts. NeuN immunohistochemistry was performed (NeuN, monoclonal, 1:1000, Chemicon), and only NeuN-immunoreactive neuronal cell bodies were counted separately within hippocampal sectors (CA1, CA2, CA3, and CA4) in four randomly placed visual fields, at 20× objective magnification (Fig. 1) using Image J software. Cell densities were transformed into z-scores, based on normal values obtained from age-matched autopsy controls. The control group was obtained after autopsy realized at the Instituto do Coração (InCor) of São Paulo and was composed by postmortem tissue of 12 cases with no previous history of epilepsy and/or neurological disease who have died from cardiac and/or respiratory complication [24].

Furthermore, all tissue specimens were qualitatively analyzed by two independent observers blinded to clinical history for HS classification according to ILAE criteria [25].

### 2.4. Statistical analyses

Statistical analyses were performed using SPSS 14 statistical software for Windows. All memory test results and neuropathological parameters were transformed into z-scores, representing the amount of deviation a score has from the mean of the control population. Results that were more than two standard deviation away from the mean expected value were considered abnormal; only negative Z-scores were relevant. A control sample for neuropsychological performance was used since it does not have a test standardization of all memory test at Brazil, and we preferred not to use the American standard scores as it is a different population to compare.

Univariate analysis of variance, Student's t-test, and Fisher's exact test were used to analyze clinical and demographic data and preoperative neuropsychological results. Correlation analyses (Pearson) were applied to check the intercorrelation of neuronal densities of different hippocampal subfields. Furthermore, partial correlation analyses, controlling the variables for epilepsy duration and neuronal density of the other hippocampal subfields, were used to verify the intercorrelation of hippocampal subfields and the correlation between memory test

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